

bonded to form one or more rings, each ring having from 3 to about 7 atoms wherein one to three atoms may be heteroatoms.

- 3 (Amended). The compound of Claim 1 wherein each Y is independently selected from the group consisting of hydrogen, methyl and ethyl; and Z is selected from the group consisting of C<sub>4</sub>-C<sub>6</sub> branched [alkanyl] ~~alkyl~~ having 2 branches, unsubstituted C<sub>3</sub>-C<sub>6</sub> [cycloalkanyl] ~~cycloalkyl~~. ↓  
or
- 5 (Amended). The compound of Claim 4 wherein R<sub>3</sub> is C<sub>1</sub>-C<sub>6</sub> straight or single-branched alkyl [or straight alkyl with a terminal cyclic alkyl, saturated or unsaturated with one double bond], alkenyl or alkynyl where the site of unsaturation is between non-terminal carbon atoms, or C<sub>3</sub>-C<sub>6</sub> [cycloalkanyl] cycloalkenyl or cycloalkynyl.
8. (Amended). The compound of Claim 7 wherein R<sub>3</sub> is selected from the group consisting of methyl, ethyl, n-propyl, i-propyl, n-butyl, 1-methylpropyl, 2-methylpropyl, 1-methylbutyl, ethoxy, [benzyl, phenethyl], cyclobutyl, cyclopentyl, [and] cyclohexyl or bonded to form benzyl or phenethyl.

## REMARKS

### Status of the Case

This case was filed as U.S. Serial No. 08/595,158, on February 1, 1996. The present invention relates to compounds having the general formula found in Claim 1 above, pharmaceutical compositions containing the compounds and methods of treating pain and inflammation using the compounds.

The specification and Claims 1, 3, 5 and 8 have been amended to recite proper nomenclature. No new matter has been added, Applicant therefore requests the amendments be entered

### Rejection Under 35 USC §102(b)

Claims 1-17 stand rejected under 35 USC §102(b) as being anticipated by U.S. Patent 5,496,853, Shiota et al., issued March 5, 1996 (Shiota et al.). The Examiner states that Shiota et al. disclose N-2,3-dihydrobenzofuranyl-ureas where the urea group is substituted at the 5, 6, 7, or 8-position. Further, the Examiner states that these are strong ATCAT enzyme inhibitors and have strong anti-hyperlipidemic and anti-atherosclerotic activity. The Examiner then concludes that since the latter (atherosclerotic) is known to be an inflammation of the arterial wall the instant utilities are the same as the claimed invention. Applicant traverses the rejection.

Shiota et al. teach a variety of dihydrobenzofuran ureas as ATCAT inhibitors. Shiota et al. does not disclose the advantages and/or the compounds with the

substitutents as currently claimed at the 7-position. In addition the Examiner's assertion that atherosclerosis is "known to be an inflammation of the arterial wall" is incorrect. Shiota et al.'s compounds are enzyme inhibitors that prevent the synthesis of cholesterol. while inflammation may be a component in the etiology of atherosclerosis, Shiota et al.'s compounds do not work in preventing inflammation. The mechanism of action for the compounds of Shiota et al. have nothing to do with inflammation. Thus, neither the compounds of the present invention nor their use is anticipated by Shiota et al.

### **Rejection 35 USC §103**

Claims 1-11 stand rejected under 35 USC §103 as being unpatentable over Shiota et al. The Examiner states that the dihydrobenzofuran-5-yl ureas as anti-inflammatories of the present invention are obvious in view of compound nos. 306, 521, 522 and 525. Applicant traverses the rejection.

Shiota et al. as mentioned above disclose dihydrobenzofurans (DHBFs) but not the DHBFs of the present invention as currently claimed. Shiota et al. disclose a myriad of compounds, none of which are close to the claimed invention with substituent as claimed by the Applicant, (especially as claimed by Applicant in Claim 2). It is commonly known that alkyl substitution is unpredictable. Thus, there is no teaching or suggestion of the compounds claimed in the present invention. Therefore, it would not have been obvious, barring hindsight by using Shiota et al., to have arrived at the compounds of the claimed invention.

In addition, as noted above, the use of the compounds of Shiota et al. for atherosclerosis does not teach the use of compounds for inflammation. Just as there is unpredictability regarding substitution in compounds, there is also unpredictability concerning use. Thus, the Claims relating to the use of the compounds of the claimed invention are not obvious in view of Shiota et al.

### **Rejection 35 USC §103**

Claims 1, 2, 12 and stand rejected under 35 USC §103 as being unpatentable over U.S. Patent 3,252,999, Herbst, issued May 24, 1966 (Herbst) in view of Shiota et al. The Examiner cites Herbst for the proposition that Herbst teaches 2-methyl-2,3-dihydrobenzofuran-5-yl groups as useful as hypoglycemic, diuretic and anti-hypertensive agents. The Examiner states that the hypoglycemic and diuretic activities are very close to the instant anti-inflammation activities. Shiota et al is cited as being of similar pharmaceutical activities. Applicant traverses the rejection.

Herbst discloses dihydrobenzofuran ureas substituted only with a methyl group at C-2 of the dihydrofuran ring. The compounds of the claimed invention are

substituted at the 3 position. The Examiner again asserts that the "similarities" in activities make the claimed invention obvious. Applicant disagrees with this assertion. Shiota et al. recognized the uncertainty in ascribing use to the compounds. "It is known that some compounds wherein benzoxazole or 2,3-dihydrobenzofuran ring is directly bonded to a nitrogen atom of a urea or amide portion can be used as an intermediate for synthesizing drugs, insecticides, vermifuges, bactericides for agriculture and gardening, herbicides, photographic materials, etc." (column 2, lines 7-12). The activities disclosed by Herbst and Shiota et al. are not the same as the claimed invention, further because of uncertainties in use, one skilled in the art would not expect the compounds of the claimed invention to be used in the treatment of inflammation.

### **Rejection Under 35 USC §102(b)**

Claims 1 and 2 stand rejected under 35 USC § 102(b) as being anticipated by Lettiere et al., *J. Med. Chem.*, 1976 (Lettiere et al.) The reference is said to disclose N-chroman-6-yl-N-optionally-substituted aryl or alkyl ureas meeting the claims of the present invention. Applicant traverses the rejection.

Lettiere et al. disclose only dihydrobenzopyrans without substitution on the dihydropyran ring and with only chloro or methyl on the benzene ring. Lettiere et al. do not teach or suggest the compounds of the claimed invention as currently amended. Applicant requests the rejection be withdrawn.

### **Rejection Under 35 USC §103**

Claims 1-17 stand rejected under 35 USC §103 as being unpatentable over Shiota et al. in view of Herbst and Lettiere et al.. Specifically the references are said to teach similar activities. Applicant traverses the rejection.

As stated above, the uses of Shiota et al. and Herbst are different than the uses of the present invention. Lettiere et al. disclose that their compounds are "related to the pharmacologically active 2,3-dihydro-2-methyl-benzofuranyl analogs. The disclosure of Lettiere et al. merely adds to the compounds which have similar use to what Herbst disclosed. There is still no disclosure in any of the references that these may be used in the treatment of inflammation. Nor is there any disclosure that because of so-called similarities in structure, there would also be similarities in uses. Therefore, no combination of the above references make the compounds of the claimed invention or their uses obvious. The rejection should therefore be withdrawn.

**Rejection Under 35 USC §102(b)**

Claims 1 and/or Claims 1 and 2 stand rejected under 35 USC §102(b) as being anticipated by U.S. Patents 4,927,824, Adler et al., issued May 22, 1990 (Adler et al.); 3,963,717, Cooke et al., issued June 15, 1976 (Cooke et al.); 4,767,779, Duggan issued August 30, 1988 (Duggan); and 4,297,490, Neumann, issued October 27, 1981 (Neumann); and PCT application WO93/03011.. Applicant traverses the rejections.

The present invention can be distinguished from all the above-identified references. First, the compounds of Alder et al are not related to those of the current application. These Alder et al. compounds are 1,3,5-triazene-2,4,6-triones not ureas. Despite the observation that the N-CO-N substructure can be found within this heterocycle, the conclusion that these compounds are therefore ureas is incorrect. The electronic, steric and conformational characteristics of the Alder et al. compounds are markedly distinct from the claimed compounds of the present invention.

Second, Cooke et al. disclose a dihydrobenzofuran urea as an intermediate for the synthesis of the compounds of interest which are furoquinazolinones. The final compound is not of any relevance to the claimed invention. Further, there is no disclosure relating to the importance of appropriate substitution on the benzene and dihydrofuran moieties of the intermediate. Neither is there any teaching or suggestion of the intermediate for any other use, particularly for anti-inflammatory activity.

Third, Duggan discloses compounds structurally distinct from the compounds of the present invention. The compounds of Duggan are viewed as carbamoyl substituted pyrazolines rather than compounds in which "one of the urea N's is part of the pyrazoline ring".

Fourth, Neumann discloses a dihydrobenzofuran thiourea as an intermediate. The compound contains none of the critical substituents on the dihydrofuran or benzene rings as claimed in the present invention.

Fifth, the structural feature in PCT application WO93/03011 is the  $\beta$ -aminoethyl substituted urea unit. The present invention does not contemplate such compounds.

In summary, none of the references cited by the Examiner anticipate the compounds as currently claimed by the Applicant.

**Rejection and Objection Under 35 USC §112**

Claims 1-17 stand rejected and the specification is objected to under 35 USC §112, second paragraph and first paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention and failing to provide an adequate description of the invention. Applicant traverses the rejection.

Claims 1, 3, 5 and 8 have been amended to better define the invention. Claims 1, 3, 5 and 8 have all been amended consistent with the Examiner's suggestions.

Applicant however, disagrees with the Examiner that the use of the term alkyl is indefinite or vague. The Examiner asserts that the meaning of alkyl is a saturated acyclic hydrocarbon group. It is well recognized that Applicant may be their own lexicographers. Applicant in the present application have definitely and distinction set forth in the specification and the claims that the alkyl may have substituents. One skilled in the art could easily ascertain the metes and bounds of the invention by reading the definitions set forth by the Applicant. Applicant believes that the definitions provided clearly define the definition without confusion.

Applicant requests clarification regarding Claim 4. The Examiner requires a correction at the end of line 3; however, Claim 4 is only 2 lines.

### CONCLUSION

Applicant has amended Claims 1, 3, 5, and 8 to better define the invention. Thus in view of the amendments and the above remarks regarding the rejections and objections under 35 U.S.C. 102(b), 103, and 112, Applicant requests that the rejections and objections be withdrawn and Claims 1-17 be considered. Applicant maintains that none of the references teach or suggest the present invention. Further, Applicant believe that the Examiner has used impermissible hindsight in rejecting the claims as being obvious. Therefore, Applicant respectfully requests that Claims 1-17 as currently claimed be allowed.

Respectfully submitted,

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